Comments on

The National Toxicology Program Substance Profile on Styrene DRAFT

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Philip Cole, MD, DrPH [1]
Professor Emeritus
Department of Epidemiology
School of Public Health
University of Alabama at Birmingham
Email: pcole@uab.edu

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[1] Full Disclosure: These comments are largely excerpted from the review paper cited here and recently submitted for publication. That paper was provided to the NTP by its sponsor, the Styrene Information and Research Center (SIRC). SIRC also has sponsored my appearance here.

Purpose

This presentation is based on a comprehensive review of the epidemiologic literature on styrene and cancer written by my colleagues and me (1).

Methods

We conducted PubMed searches for relevant papers using various search terms. These searches were supplemented with a review of materials cited by IARC (2) and in the NTP's Final Report on Carcinogens Background Document for Styrene (3). Our paper cites 61 references, including 25 with original data. However, our analyses rest primarily upon seven papers which include or update findings from 18 earlier publications. The papers that the styrene Substance Review Group (SRG) and that we relied upon are the same.

We compiled and presented data for seven cancers of greatest interest including lymphohematopoietic (LHP) cancers on "all causes of death" and on "all cancer". The DRAFT Substance Profile for styrene is focused on the LHP cancers and particularly on non-Hodgkin lymphomas (NHLs) and leukemias in the styrene-based reinforced plastics industry and in the production of styrene-butadiene rubber (SBR). Because of time limitations, this presentation is limited to the same diseases.

Results

Overall Results - Table 1 shows results for the six studies (4-9) from which we could isolate data for the LHPs, with the virtual exclusion of the NHLs and the leukemias. This category is in effect a combination of Hodgkin disease and multiple myeloma. Only study 4 with an SMR of 1.97 (95% CI: 1.02-3.45) shows an elevation and it is of borderline statistical significance. For the three industry groups, combined, the SMR for these LHPs is 0.97 (0.81-1.16).

Table 2 shows findings from six (4-7,9,10) of the studies with data on the non-Hodgkin lymphomas (NHLs). Only study 10 (the smallest study) has a significantly elevated SMR, 5.36 (1.10-15.65). There was no significant excess of NHL for any of the three industry groups and, overall, the SMR was a non-significant 1.07 (0.90-1.27).

Table 3 shows findings from the seven (2-8) studies with data on leukemia (all forms combined). There is no significant elevation of leukemia in any of the seven studies, in any of the three industry groups, or overall SMR = 1.08 (0.89-1.31).

Table 4 shows an important subset of the available data. It presents results for the two disease groups of major interest, leukemia and non-Hodgkin lymphoma, from the four studies that had at least one overall positive finding. This table emphasizes a major point: even the most positive findings available, in the aggregate, can not provide evidence of an association strong enough to support a causal relationship.

Internal Analyses – The SRG agrees with our view that the overall findings of the epidemiologic research is negative and provides no support for considering styrene as a human carcinogen. The SRG then goes on to consider "*internal*" analyses. In doing this they emphasize the findings of Kogevinas et al 1994 (6), Kolstad et al 1994 (7) and Delzell et al 2006 (9). The SRG gave considerable weight to these "internal analyses" in evaluating the relationship between styrene and the LHP malignancies. We have done the same and have evaluated leukemia and NHL frequency in relation to six different measures, or descriptors, of exposure. These are: 1) duration of exposure, 2) average exposure, 3) cumulative exposure, 4) peak exposure 5) time since hire and 6) early v. recent first exposure. Not all indices were available for all studies and not every disease group was so evaluated in each study.

Table 5 provides an overview of the findings on internal measures of styrene exposure according to study and disease group. An entry of "No" means that the study-metric-disease relationship was not supportive of causation. When interpreting the overall findings in table 5, these four points should be kept in mind:

1. For each of the two disease groups there are only three (out of 10 possible) measures with positive findings. Further, for each disease group one of the positive findings (from the SBR (9) study) is weak and possibly due to residual confounding by butadiene and/or dimethyldithiocarbamate.

2. For neither disease is any measure positive in more than one study.

3. These data came from the studies selected by the SRG for this purpose from among all studies. They were selected despite the fact that all three studies have overall null findings for both disease groups.

4. Scientific judgment and common sense indicate that in a study with an overall null result, associations based on internal analyses can not be interpreted confidently as real associations, much less as causal relationships, unless those analyses produce findings that are strong and consistent. That is not the case here.

Conclusion

The epidemiologic studies of styrene and cancer relied upon by the styrene research group and by us provide no support for the suggestion that styrene is a human carcinogen.

Legends for Tables

1. LHP – Excluding NHL and Leukemia.
   Observed and expected numbers of deaths (cases), SMRs and 95% confidence intervals according to study.

2. Non-Hodgkin Lymphoma.
   Observed and expected numbers of deaths (cases), SMRs and 95% confidence intervals according to study.

3. Leukemia.
   Observed and expected numbers of deaths (cases), SMRs and 95% confidence intervals according to study.

4. Positive Findings.
   A compilation of positive findings from Tables 2 and 3.

5. Summary of Internal Analyses.
   An overview of internal analyses for three studies cited in the NTP styrene substance profile.

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